minimal or no response) adds rituximab to lenalidomide. The results of this trial indicate that CLL patients who have initially received lenalidomide can have enhanced clinical responses with the addition of rituximab (Chanan-Khan, verbal communication, July 2008). Until there is a clear dissection of the exact mechanisms of rituximab-mediated clearances of CLL B cells, it would seem premature to alter current strategies. However, this work does make a very strong case for further studies of monoclonal antibodies in xenograft mouse models where the timing of lenalidomide and other monoclonal antibodies targeted to CLL B cells is tested.

This study also found that lenalidomide-mediated internalization of CD20 can be used to enhance the ability to deliver oligonucleotide-based therapy by using CD20 immune liposomes. The investigators are to be congratulated for recognizing that the internalization of CD20 could be a novel approach for delivery of treatment vectors, such as microRNA or siRNA, that can target critical molecules in CLL B cells. This latter finding underscores the fact that the investigation of drugs such as lenalidomide must be continued not only to determine the exact nature of the mechanism of action in the presence or absence of other drugs/monoclonal antibodies but also in the context of specific diseases. In total, this work has shown the “yin and yang” of lenalidomide: decreases in rituximab-mediated ADCC of CLL B cells by NK cells when CLL B cells are preincubated with the drug, increases in ADCC if NK cells are first exposed to lenalidomide, and increases in CD23 and CD38 but reduced membrane levels of CD20 via internalization. Further work in CLL and other B-cell malignancies that evaluate the key mechanisms of action for lenalidomide toward leukemic/lymphoma cells are surely going to uncover critical information for the clinical trialist.

**Conflict-of-interest disclosure:** The author declares no competing financial interests.

---

**REFERENCES**


Dis-Abl-ing CD40 buys toxic assets

John Gordon UNIVERSITY OF BIRMINGHAM

In this issue of Blood, Hallaert et al show that clinically approved c-Abl inhibitors reverse the protection against conventional chemotherapeutic drugs afforded to CLL cells from prolonged CD40 signaling.

Chronic lymphocytic leukemia (CLL), though well understood molecularly and functionally, essentially remains incurable. In vivo survival niches probably contribute to a surprisingly poor performance from drugs that seem very promising in vitro. Bone marrow stroma, blood-borne nurselike cells, and lymph node follicular dendritic cells are all culprits in the conspiracy. At the heart of their operations lies the induction of antiapoptotic proteins, including the “usual suspects” of Mcl-1, Bcl-2, and Bcl-xL. One avenue of attack is to target the survival proteins directly as recently described using BH3-neutralizing AT-101. In this issue of Blood, Hallaert et al have masterminded an alternative strategy that interrupts the signaling processes that promote CLL protection. To guide them toward the guilty pathway, a neat piece of detective work was employed.

First, they constructed a survival niche: CD154-transfected fibroblasts furnishing both CD40 stimulation and a range of stromal factors. CD40 ligation affords, in all manner of B cells, substantial protection to both default and deliberately provoked apoptosis, and CLL is no exception. In addition to confirming previously described CD40-driven antiapoptotic changes in CLL populations, the authors identified for the first time a reduction in the proapoptotic protein Bim-EL. It was known from other systems that ERK-signaling could alter levels of Bim-EL protein, and they went on to show that not only did CD154 stimulate ERK phosphorylation in CLL cells, but also that inhibiting ERK activity negated the ensuing Bim-EL decline. However, ERK proved an innocent bystander when considering resistance to therapeutic drugs. Thus, even with ERK incapacitated, fludarabine, bortezomib, and others were all powerless to outmaneuver the defenses bolstered by CD40 and stroma.

The authors next trained the spotlight on the increased Mcl-1 protein expression they had noted. This is when c-Abl began to audition for the leading role. Already a star of the Philadelphia chromosome, survival signaling via dysregulated Abl underpins pathobiology of chronic myeloid leukemia (CML). Not only Mcl-1 but also other antiapoptotic signatures from niche-protected CLL cells conformed to those emanating constitutively from BCR-Abl. With all the pieces now so elegantly in place, it does not require a Lieutenant Columbo to pronounce the denouement: c-Abl inhibitors used so successfully for treating CML likewise overcame conferred resistance to underperforming therapeutic drugs in CLL. Both widely used imatinib (gleevec) and even more so second-generation dasatinib (spryel) rebooted CLL cells to drug sensitivity. This desired outcome was accompanied by a requisite reversal of the antiapoptotic profile imparted by the survival niche. Neither IgVH mutational status nor p53 dysfunction tempered the success. As an added bonus, the authors were able to recapitulate findings on blood CLL cells with samples from lymph node biopsies.

This is an exciting advance. The data are persuasive and internally consistent. Questions do remain but not necessarily of a quality to warrant concern with respect to therapeutic options. The authors themselves confess to their model being “supraphysiological.” While B cells are constitutively programmed for CD154 receptivity, the opportunity for ligand

REFERENCES

Comment on Hallaert et al, page 5141

GATA-1–regulated genes has not been described. Thus, the findings of Elagib et al could provide new insight into the pathogenesis and, conceivably, the treatment of this human myeloproliferative disorder.

Conflict-of-interest disclosure: The author declares no competing financial interests.
GATA-1: one TEF customer

Stephen J. Brandt